DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Joe Barton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515-6115

APR 14 2004

Dear Mr. Chairman:

Thank you for your letter of March 24, 2004, concerning the Food and Drug Administration's (FDA or the Agency) decision to issue its March 22, 2004, *Talk Paper* entitled, "FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children" and events surrounding an FDA internal consult prepared by Andrew D. Mosholder, M.D., M.P.H. on this issue.

Certain of the enclosed documents contain trade secret, commercial confidential, or other privileged information protected from disclosure to the public under the Freedom of Information Act (Title 5, United States Code [U.S.C.] section 552), the Trade Secrets Act (18, U.S.C. section 1905), and FDA regulations. The Committee should not publish or otherwise make public any such information. We would be glad to discuss with the Committee staff the protected status of any specific information. IMS Health and ADVANCEPCS utilization data is contained in a memo prepared by Dr. Mosholder. FDA obtained this data under contracts with IMS Health and ADVANCEPCS. The terms of the contracts stipulate that the utilization data cannot be released to the public. We request that the Committee not publish or otherwise make public this information. Finally, as discussed with Committee staff, we have redacted personal privacy information from the enclosed documents.

Your letter expressed a concern about evidence or reports developed or obtained by FDA staff regarding possible suicide-related adverse events associated with the use of specific drugs and also a concern that information relating to using these drugs safely in pediatric populations may not have been made public in a timely way. We want to assure you that at this time, based on our review, we do not believe that to have been the case.

FDA fully recognizes the critical public health importance of a possible link between use of antidepressant drugs in children and suicidal thoughts or behavior. Our goal has been, and remains, to carefully evaluate all the available data in a scientifically rigorous manner before reaching a conclusion. Our judgments in this matter will strongly influence how antidepressants are prescribed in children in the future. What we must do is give parents and physicians the very best information, because the health risks of incorrect conclusions are potentially great. In

conducting its evaluation, FDA has followed its usual practice of engaging the expertise of experienced reviewers from different parts of the Agency and from outside sources to ensure that these issues are rigorously examined. The collective input from the various expert sources has been the basis for developing the Agency's current position on this issue.

Background on FDA's Review of Antidepressant Drugs

To place FDA's recent public announcements on this issue in proper perspective, it is important to briefly review the history of our examination of the issue of a possible link between the use of antidepressants in children and suicidal thoughts or behavior. Under the pediatric exclusivity provisions of the Food and Drug Administration Modernization Act, FDA issued requests to manufacturers of antidepressants for studies of these drugs in children. During our review of a supplemental new drug application submitted by GlaxoSmithKline (GSK) that contained the requested studies of the use of Paxil (paroxetine) in children, reviewers in the Division of Neuropharmacological Drug Products (DNDP) of FDA's Center for Drug Evaluation and Research (CDER or the Center) noted a greater number of adverse events that were coded under the term "emotional liability" in the group of patients treated with Paxil compared to placebo in some, but not all, of the studies. The reviewers noted that the actual events that were coded under this term included suicide thoughts and attempts as well as other forms of non-suicidal self-injurious behavior. In an effort to better understand these events and to further explore the extent of episodes of suicidal thoughts or behavior in children treated with Paxil, DNDP requested that GSK reanalyze their data and better characterize the adverse events that were identified under the term emotional liability.

GSK submitted their report to the Center on May 22, 2003, and on June 6, 2003, Dr. Russ Katz, the director of DNDP, requested that the Office of Drug Safety (ODS) perform a consultative review of the newly submitted safety data. Dr. Katz requested that Dr. Andy Mosholder be assigned as the primary reviewer for the consult since Dr. Mosholder had previously been involved in reviewing data on the safety of antidepressants when he worked as a reviewer in DNDP.

Following its initial review of these new data for Paxil, FDA issued a *Talk Paper* on June 19, 2003, that stated: "Although the FDA has not completed its evaluation of the new safety data, FDA is recommending that Paxil not be used in children or adolescents for the treatment of major depressive disorder (MDD)." FDA also expanded its investigation of a possible link between use of antidepressants in children and suicidal thoughts or behavior by requesting data similar to that submitted by GSK from the manufacturers of eight other antidepressant drugs that had been studied in children. On July 22, 2003, requests for data were sent to the manufacturers of the following drugs: Prozac (fluoxetine), Zoloft (setraline), Luvox (fluvoxamine), Celexa (citalopram), Wellbutrin (bupropion), Effexor (venlafaxine), Serzone (nefazodone), and Remeron (mirtazapine). These data requests from the Center, and the submissions from the manufacturers in response to them, have provided the core data on which the Agency has developed its scientific review of this issue.

As the reviewers in DNDP and ODS began conducting their more detailed reviews of these new safety data and carefully evaluated the narrative descriptions of the reported adverse events, the

reviewers identified several new issues for further evaluation. These additional issues included the following matters:

1. A number of the adverse events classified under the category "possibly suicide related." For example, one child had hit her head with her hand, a number of children had engaged in superficial cutting behavior, and a number of children had ingested small numbers of pills in sight of parents, which while potentially of concern, taken alone, would not necessarily be an indication of suicidal behavior.
2. Although there were more adverse events that were characterized as "possibly suicide related" in patients taking the antidepressant drug compared to those taking placebo in some of the trials in children, this pattern was not consistently observed across all of the trials, even within individual drug programs.
3. There was a concern that due to the methods used by the manufacturers in searching their database, the possibility existed that not all adverse events of possible interest in addressing the potential risk of suicidality had in fact been captured.

To more fully evaluate these new issues, the DNDP determined that additional data searches and analyses were necessary. To further address issue 1, whether the reported adverse events represented suicidal behavior, Agency staff determined that an independent panel of experts in suicidology should be convened to carefully evaluate and reclassify the reported adverse events. DNDP arranged for this work to be performed under a contract with Columbia University and this review is ongoing. Once the reclassification of the adverse events is completed, the Center believes that it may be able to conduct more definitive analyses of the data. To further address issues 2 and 3, on November 24, 2003, DNDP requested additional data from the manufacturers of the other antidepressants that had been studied in children. The division specifically requested individual patient data for all the studies. The availability of these more detailed data would permit a more refined analysis, taking into consideration possible imbalances across study groups in these trials, and a more complete accounting of the search methods employed by these companies to ensure that possible cases of suicidality had not been overlooked. We expect these additional analyses to be completed this summer, and we will present these new analyses to the Advisory Committee for discussion. We expect this second Advisory Committee meeting to occur in late summer.

While the Center was conducting its more in-depth review of the data from the pediatric clinical trials, planning was also under way to hold an Advisory Committee meeting February 2, 2004, to review the post-marketing safety reporting for a number of products that had been granted pediatric exclusivity. A review of the post-marketing safety data is mandated for such products under the Best Pharmaceuticals for Children Act. One of the drugs scheduled for review at the February 2, 2004 Advisory Committee meeting was Paxil. In planning for the discussion of the safety of the use of Paxil in children at the Advisory Committee meeting, the Agency initially intended to broaden the meeting to include a discussion of the Agency's review of the safety concerns that arose from the data from studies of the use of antidepressants in children. However, as the reviews and meeting planning progressed, it became clear that the additional analyses of the data from the clinical trials of antidepressants in children would not be complete in time to present the Agency's final assessment of these data at that meeting. Therefore, the Agency decided to proceed with the plans to discuss the post-marketing safety data for Paxil at

the meeting, to brief the Advisory Committee on the Agency's progress in evaluating the data from the clinical trials of antidepressants in children, and to solicit advice and comment regarding the Agency's plans for further analyses. The plan included returning to the Advisory Committee for another meeting after the Agency's more definitive analyses of the clinical trial data were complete to solicit Advisory Committee input prior to further regulatory action.

While CDER was moving ahead with plans for the February 2, 2004, Advisory Committee meeting, Dr. Mosholder was nearing completion of his review of the data from the clinical trials. Based on his review, he believed that the available data were sufficient to reach a conclusion about an association between the use of antidepressants and suicidality in children and to recommend that additional regulatory action would be appropriate without the need for the more in-depth case classification or analyses that had already been initiated by DNDP. Dr. Mosholder shared his conclusions with his supervisors and with the rest of the team involved in reviewing this issue. However, the other members of the review team, including his direct supervisors, did not agree with his regulatory conclusion that no further analyses were needed and continued to believe that additional analyses should be conducted before the Agency could reach a conclusion on these data. There was a discussion within the review team as to whether Dr. Mosholder's regulatory conclusions on the data should be presented in some form at the February 2, 2004, meeting. After considering the issue carefully, CDER staff decided that the data from which Dr. Mosholder reached his conclusions would be presented to the Advisory Committee meeting and that they would acknowledge as part of their presentation to the Committee that some reviewers had reached a conclusion that the data at this time were sufficient to conclude that there was a link between antidepressant use and suicidality in children. However, given the Agency's concerns regarding the limitations of the data and the plans to pursue case reclassification and more in-depth analyses, CDER decided that having Dr. Mosholder present his conclusion to the Advisory Committee, with the appearance that it was an Agency determination, would be potentially harmful to public health as it might lead patients who were actually benefiting from the use of these drugs to inappropriately discontinue therapy. CDER believed that disclosure of the available data to the Advisory Committee at the meeting along with a description of the limitations of those data in supporting a definitive conclusion, as well as a description of the Agency's plans to further evaluate the data was the best way to serve the public health on this very complex and important issue. The Agency takes very seriously its responsibility to the public to find the right answer to this question, and a premature conclusion that the drugs are harmful that does not hold up to more careful review would be a disservice to the public health given the serious, and potentially life-threatening nature of severe depression.

At the Advisory Committee meeting, Dr. Katz made an opening presentation of the issues and questions and made clear that some within the Agency believed that the data were conclusive. Dr. Tom Laughren from DNDP gave a more extensive presentation in which he carefully reviewed the available data and its strengths and weaknesses. Dr. Laughren also described to the Committee the Agency's plans to further evaluate the data and to return to the Committee for a more definitive review once those analyses were complete. Dr. Laughren specifically presented the same data from which Dr. Mosholder had reached his conclusions and the same data from which the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK reached its conclusions.

Although Dr. Mosholder did not present the clinical trial data or his conclusions at the Advisory Committee meeting, he is a member of the review team for this project and did make a presentation to the Committee regarding his evaluation of the postmarketing safety data for Paxil. The presentation of the clinical trial data by the staff in DNDP and the postmarketing safety data by the staff in ODS is fully consistent with CDER's normal, approach to the division of these review responsibilities.

In summary, the Center's review process involves a multidisciplinary approach to ensure that expertise from various areas of the Agency and from outside groups is brought to bear on an issue to ensure that a comprehensive and rigorous scientific analysis is completed that serves as the basis for the Agency's conclusions and actions. The review process honors and explicitly encourages individual reviewers to share their conclusions and recommendations with the review team to help inform the Center's decisions and actions. In some cases, the opinion of an individual reviewer may not be consistent with the Center's position on an issue. This occurs regularly and is to be expected in a large scientific organization that values open discussion of issues. In such cases the Center has procedures in place to ensure that the reviewer's position is documented, fully considered, and addressed by managers as part of the process.

Those procedures were followed in this case and, in the interest of full disclosure and open debate, the Agency ensured that the data were presented for public review. We specifically acknowledged at the public meeting that some within the Agency had reached different conclusions. The Advisory Committee fully discussed the available data regarding the safety of the use of antidepressants in children and concurred with the Agency's plans for further analyses prior to reaching more definitive conclusions. At the meeting, based on the presentations, the Advisory Committee recommended that FDA take interim steps to warn physicians, patients, and parents of the potential safety concern and the need to carefully monitor patients for evidence of suicidal thoughts or behavior while taking antidepressant drugs. The Agency concurred with the Advisory Committee's recommendations and issued a Public Health Advisory on this issue on March 22, 2004, along with a request to each of the manufacturers that they update the labeling for their product to reflect this information. The Agency is continuing its review of this important issue and plans to return to the Advisory Committee for further discussion when the additional analyses are complete later this summer.

FDA raised serious questions about the antidepressants, took the initiative in acquiring the relevant data, and has proceeded with careful analyses of the data from different perspectives inside and outside the Agency. The assessment of whether the antidepressant drugs under review increase the risk of suicidal thinking or behavior is critically important to patient safety. FDA's assessment on this issue is designed to achieve the most scientifically rigorous review possible.

In the meantime, we recognize the important role of Congress and the Committee, and share the objective of assuring an open and transparent process for evaluating these potential safety concerns. In response to your March 24, 2004, letter requesting a large voluume of materials, information and data, the Agency has been working closely with Committee staff to produce the necessary information. On April 1 and April 13, and April 14, 2004, in conversations between Patrick McGarey of FDA's Office of Legislation and Kelli Andrews and Alan Slobodin of the

Committee staff, we agreed to partially respond by providing responses to questions numbered 11 and 12 and a partial response to questions 1, 2, and 4. We have restated your questions followed by our answer. We sill continue to work with Committee staff on this document request, and may provide additional responsive materials to these questions if they are identified.

1. **All records provided by or to the FDA in connection with the February 2, 2004 FDA Advisory Committee meeting involving the Psychopharmacological Drugs Advisory Committee (PDAC) and the Pediatric SubCommittee of the Anti-Infective Drugs Advisory Committee (Peds AC), including, but not limited to, records relating to the planning of this meeting and its agenda.**

Based on conversations with Committee staff, we are providing records provided by or to the Advisory Committee Staff from outside parties related to the February 2, 2004, FDA Advisory Committee Meeting. The documents are enclosed at Tab A. As we discussed with Committee staff, due to the very large volume of documents that are responsive to this question, and in light of the difficulty we had reviewing and redacting personal privacy information and producing these documents by the time we issued this letter, we are providing a partial response at this time. We will discuss with Committee staff the timetable and need to produce further documents in response to this question.

As part of the meeting process, we published a transcript and documents. These documents also may be relevant to your inquiry and can be found at:
http://www.fda.gov/cder/drug/antidepressants/default.htm

2. **All records of Dr. Andrew Mosholder, Dr. Mary Willy, Dr. Russell Katz, Ms. Anne Trontell and Dr. Thomas Laughren, relating to efficacy and safety of anti-depressants in the pediatric and/or adolescent population, including, but not limited to, all draft or final reports, internal correspondence, e-mails and notes concerning pediatric or adolescent anti-depressant clinical trials and any records relating to spontaneous reports (AERS system) on the same issue.**

Based on conversations with Committee staff, we are providing the records compiled by Dr. Andrew Mosholder beginning with records created on January 1, 2003. The documents are enclosed at Tab B.

4. **All records relating to GlaxoSmithKline's submission of data analyses in pediatric/adolescent clinical trials involving Paxil, including, but not limited to, all submissions contained as attachments to their May 22, 2003 letter to the FDA.**

Based on conversations with Committee staff, we are providing records from the NDA file beginning with records created on October 10, 2002. The documents are enclosed at Tab C. In particular, please note that these materials contain or are reasonably likely to contain trade secret, commercial confidential, or otherwise privileged information that would not be subject to public disclosure under the Agency's FOI regulations.

11. **A listing of all the pediatric/adolescent clinical trials involving anti-depressants that the FDA received data for which there was an obligation for the company to submit the data to the FDA. For each such trial, include the following information:**
    a. **Name of the company;**
    b. **Name of the anti-depressant;**
    c. **Date when pediatric clinical trial data was submitted to the FDA;**
    d. **Date when pediatric clinical trial was completed by company;**
    e. **Summary of FDA's "response" to the clinical trial and what, if any, regulatory action FDA took with respect to approving the particular drug for an indication in the pediatric population.**

We have provided this information in chart form at Tab D.

12. **State the person(s) at FDA responsible for evaluating and providing a written analysis of the data that was requested by FDA, in the summer and fall of 2003, from various manufacturers of anti-depressants who performed clinical trials in children.**

Dr. Andrew Mosholder of the Office of Drug Safety was responsible for evaluating the summary data from the pediatric clinical trials on antidepressants that was submitted in response to the Agency's July, 2003 letters. Drs. Tarek Hammad and Judy Racoosin from the Safety Group within the Division of Neuropharmacological Drug Products have responsibility for analyzing the patient-level data submitted by sponsors in response to the Agency's October, 2003 request for these electronic data sets. The analysis of these patient-level data are tied to the reclassification of clinical cases is accomplished by the expert panel that has been assembled by our consultants at Columbia University.

Thank you for your interest in this matter. A similar letter is being sent to Chairman Greenwood without the enclosure. If we can be of further assistance, please let us know.

Sincerely,

Amit K. Sachdev
Associate Commissioner
for Legislation

ACTING

Enclosures